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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,915	03/23/2004	Frances Louisa Titus	48170.00040/PC832	4427

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FOX ROTHSCHILD, LLP
997 LENOX DRIVE
LAWRENCEVILLE, NJ 08648

EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,915	TITUS ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-6,16-20,31-35 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-15,21-30 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0805, 1206,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-43 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II and LMP-1 and HIV-TAT for examination in the reply filed on 8/13/07 is acknowledged. The traversal is on the ground(s) that a search of Group II and IV would not be burdensome because search the methods of using the protein would yield results of the protein as well. This is not found persuasive because the product and method of using are patentably distinct for reason given in the previous office action. Briefly, the polypeptide of group IV may be used to in the method of producing antibody, whereas the method of promote bone formation, may be practiced using materially different agent, for example, using mesenchymal stem cells and culturing said cells under proper condition. As such, the product of Group IV and the method of using of Group II are patentably distinct. And a search of both groups in a single application would have been burdensome.

Applicants further argue that the election of the sequences are improper because they are recited in Markush type claims, and share substantial structure and utility of promoting bone growth and cartilage growth. Based on the admission of the record that SEQ ID NO: 1-8, and LIM-1 and LIM-3 share substantial structure and utility, in other words, they are obvious variants of each other, they will be examined together.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-6, 16-20, 31-35, 41-43 are withdrawn from consideration for being directed to non-elected subject matter. Claims 7-15, 21-30 and 36-40 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-15 and 36-40 are rejected under 35 U.S.C. 103(a) as being obvious over Hair et al (US6521750) or (US 858,431).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR

1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or mesenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). Hair et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell

types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation based on the combined teaching of Hair et al. and Nagahara et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 7-15, 21-30 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boden et al. (Endocrinology 1998, vol. 139, no.12, pages 5125-5134), in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998. Vol.6, pages 306-317)

Boden et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (page 5133, Figure 9). Boden et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization. Boden et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see page 5131, Figure 6). Boden et al. also demonstrate that LMP induces genes such as BMP-2 expression and thus is an important regulator for osteoblast differentiation (see page 5132, 2nd col., 1st paragraph).

However, Boden et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide. Boden et al. do not each LMP induces proteoglycan production in a mammal.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

van Beuningen et al. teach that the synthesis of proteoglycan including aggrecan is increased following BMP-2 injection to the knee of a rat model (see page 309, 2nd col., 1st paragraph)

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation based on the combined teaching of Boden et al. and Nagahara et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Boden already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Moreover, since Boden demonstrates that BMP-2 is increased up to 38 fold at protein level following LMP expression, and van Beuningen et al. have shown that proteoglycan level is increased following BMP-2 injection in an animal model, it would have been reasonable for an ordinary artisan to expect that following administration of TAT LMP to a mammal, the proteoglycan synthesis will be induced. Making the fusion protein

and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,858431, in view of Nagahara et al.

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). Hair et al.

further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation based on the combined teaching of Hair et al. and Nagahara et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that

LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 7-11, 36-40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,521,750, in view of Nagahara et al.

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). Hair et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective

amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation based on the combined teaching of Hair et al. and Nagahara et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using

hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joe Woitach Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER